

Supplementary Note

The GRACE 2.4 software package performs the crystal structure prediction (CSP) in two parts, i) tailor-made force field¹ is parameterized from scratch with the Force Field Factory module, ii) actual CSP within the CSP Factory module, as shown in Supplementary Figure 1. The workflows of both modules are fully automated. A feedback loop between CSP Factory and Force Field Factory allows the use of preliminary crystal structure prediction results to improve the force field accuracy. The tailor-made force field uses fixed atomic point charges calculated from bond increments and atomic charges (for atoms with a formal charge), isotropic Lennard-Jones-9-6 van der Waals interactions, harmonic bond stretch and angle bend terms, overall torsions and overall inversions. All force field parameters are fitted simultaneously to ab initio reference data generated at the DFT-D level of theory. The empirical dispersion correction was developed at AMS². The DFT part of the energy calculations, as part of CSP, is performed either with VASP³⁻⁵ or TURBOMOLE⁶. Reference data for ionic species are generated in the COSMO approximation. Larger molecules are automatically cut into chemically reasonable fragments, which are then parameterized. In such a case, no reference data are generated for the complete molecule in the initial force field parameterization procedure. Subsequently, additional data for the complete molecule from a preliminary crystal structure prediction can improve the force field accuracy by 10-20%.

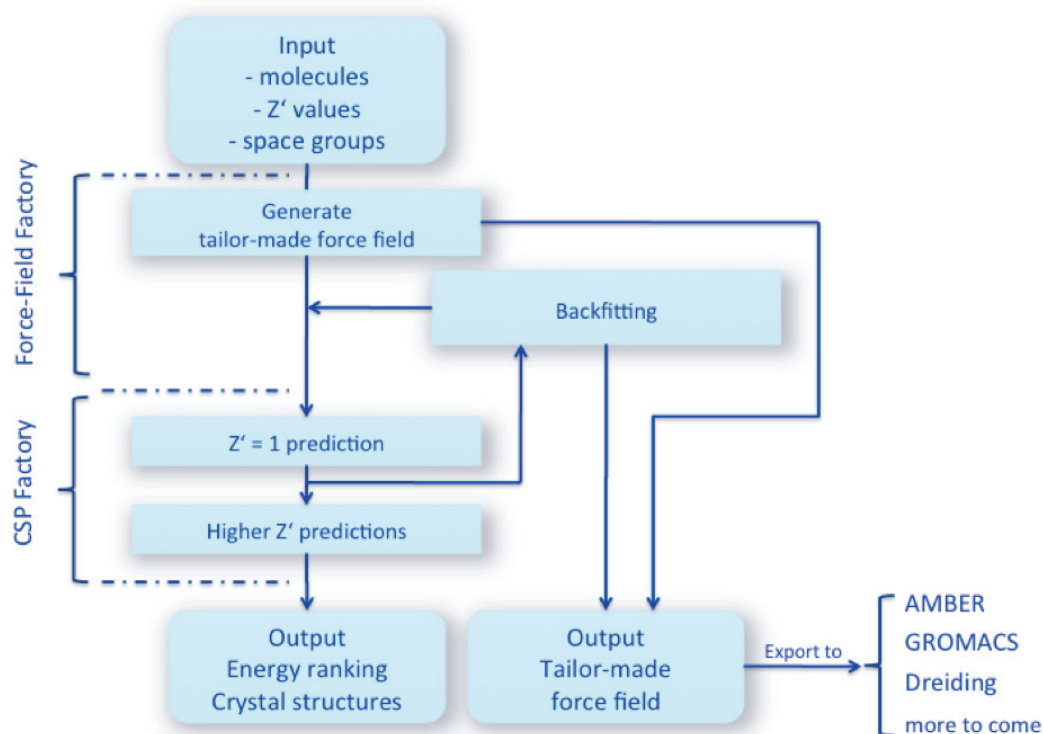
As described in the main text the crystal structure prediction with the CSP Factory uses a three-step procedure shown in Fig. 1-a. Statistical methods are used to control the completeness of the three-step procedure. The energy accuracy at each step is assessed by comparison with the

energies obtained at the next step. This way, standard deviations σ_1 and σ_2 are obtained for the force field energies of the first step and the coarse DFT-D energies of the second step, respectively. The user typically specifies an energy window, Δ , for the last step, in which the crystal structure generation should be quasi-complete. In the intermediate step, a larger window of $\Delta + n_2 \sigma_2$ is used, and for the initial structure generation step with the tailor-made force field the energy window $\Delta + n_1 \sigma_1$ is even larger. For $Z' = 1$ the standard choice is $n_2 = 3$ and $n_1 = 4$. In the first and the second step, statistical considerations are used to estimate the number of lattice energy minima and a step is considered complete for $Z' = 1$ when 99% of all structures have been generated. All structures found in the energy window of step 2 are further processed in step 3.

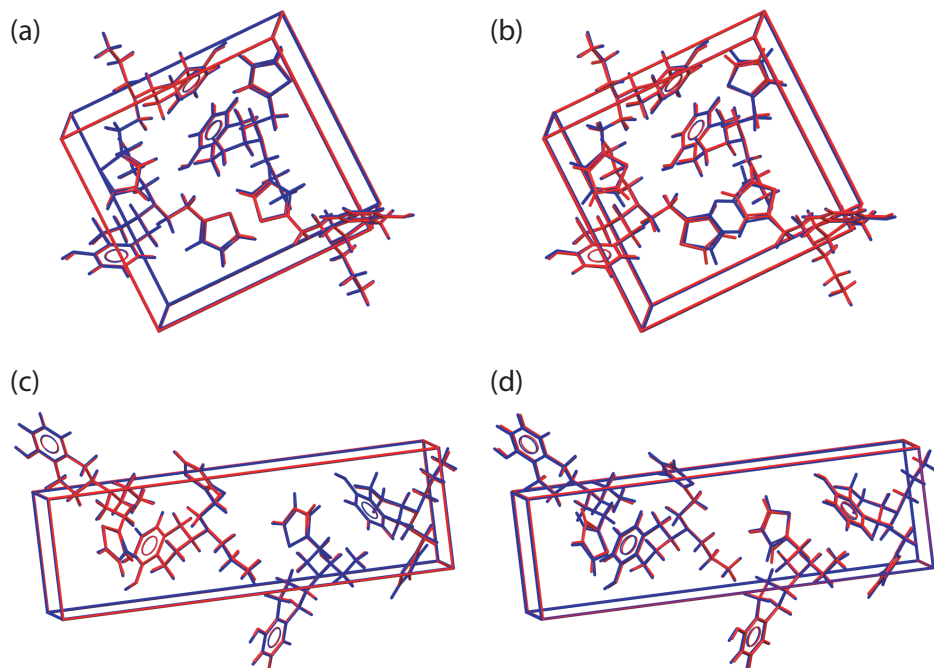
The accuracy of the TMFF after backfitting was $0.82 \text{ kcal mol}^{-1}$ per molecule. In step 1, 26 crystal structures were generated within a 4.7 sigma window at a level of completeness of 99.0%. To assess the completeness of the first step, statistically independent generations of each lattice energy minimum are counted and two completeness estimates are calculated, one based on the average number of hits and the other one based on the number of structures that are hit only once. In the second step, it would be too CPU time consuming to optimize the lattice energies of all crystal structures in the target window of the first step. Instead, statistical correlations are built up between structural similarity and the behavior upon optimization, and between the DFT-D force calculated for each force-field optimized structure and the behavior upon optimization. These considerations result in various energy estimates with standard deviations that are used to estimate the number of lattice energy minima in the target energy window of the second step. Thus 26 structures were fully optimized at DFT-D level with energy accuracy of 0.002. In step 3 (final

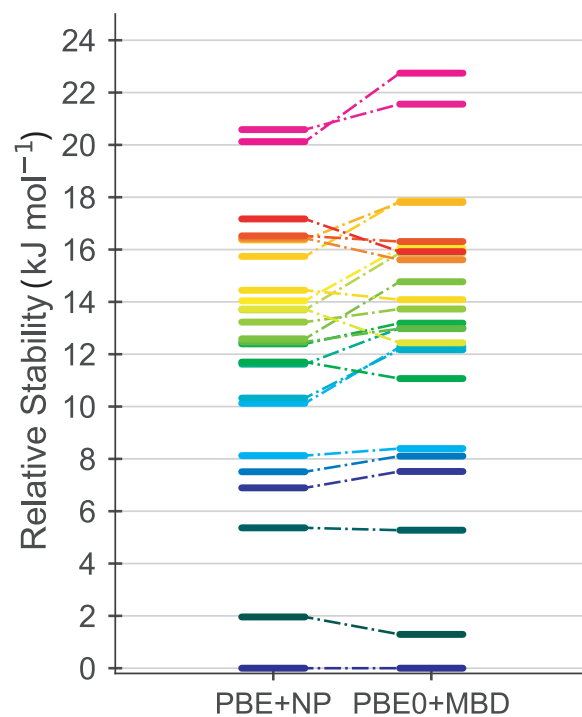
lattice-energy optimization) 25 structures were processed. The energy-density diagram for the 25 computer-generated from step 3 were shown in Fig. 1-b.

Supplementary Figures

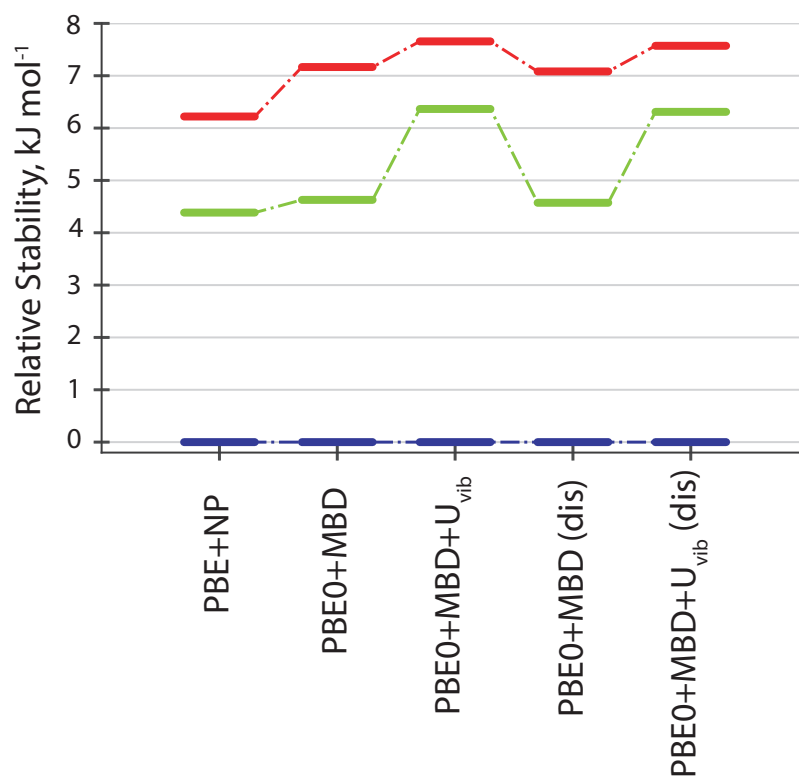


Supplementary Figure 1: **Force Field Factory and CSP Factory in GRACE**

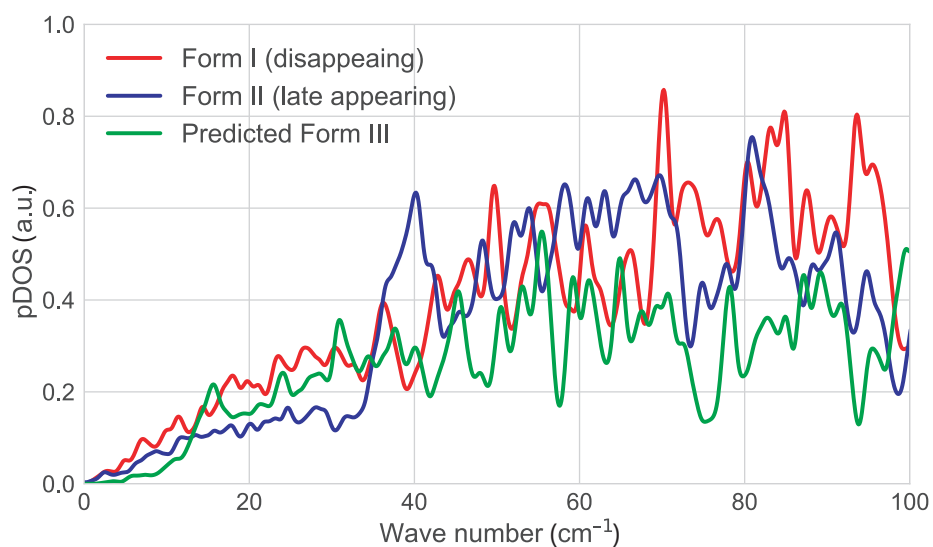




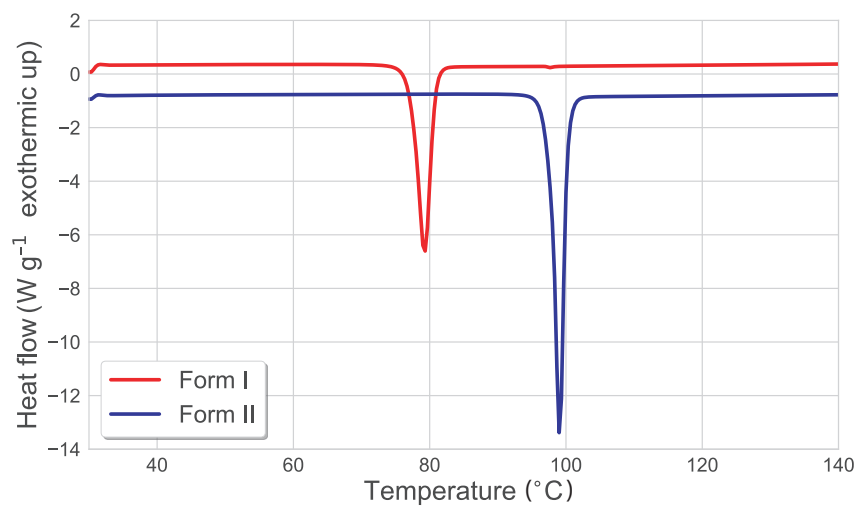
Supplementary Figure 3: **Comparison of Stability Rankings of Rotigotine.** Stability ranking of the 25 predicted structures based on PBE+NP and PBE0+MBD energies.



Supplementary Figure 4: **Stability Rankings of Rotigotine.** Stability rankings based on total energy (PBE+NP, PBE0+MBD), total energy including vibrational enthalpy (PBE0+MBD+ U_{vib}) with/without configurational disorders.



Supplementary Figure 5: **Phonon Density of States**. The pDOS of Rotigotine forms I, II, and predicted form III up to a frequency of 100 cm^{-1} .



Supplementary Figure 6: **DSC Curves** from which the relative enthalpy curves of both rotigotine forms have been calculated. Curves have been shifted vertically for clarity.

Supplementary Discussion

Supplementary Figure 3 shows a comparison between PBE+NP and PBE0+MBD for the 25 predicted structures. It can be seen that the stability ordering of forms I, II, and predicted form III remains unchanged despite slight numerical differences in relative stability. However, stability orderings change between the methods for structures with relative energies higher than 10 kJ mol⁻¹.

Next we also performed calculations with disordered structures. In both experimental polymorphs the thiophene ring exhibits two-fold disorder, and this disorder is reproduced in the crystal structure prediction study in the form of pairs of related structures. If the two configurations have energies E_0 and E_1 , and assuming that they are occupied independently, the free energy correction due to the configurational entropy can be calculated as $RT \ln q$, where R is the universal gas constant, T is temperature (here 300 K), and q is the partition function $q = \sum \exp((E_1 - E_0)/RT)$. Supplementary Figure 4 shows the stability ranking when configurational disorders were taken into account. As can be seen disorders change the results neither qualitatively nor quantitatively. The equation relating the solubility ratio of two polymorphs in the same solvent

$$K_I/K_{II} = \exp[-\Delta F/RT] \quad (1)$$

is derived as follows: Given two dissolution reactions for Rotigotine form I (Rot_I) and form II (Rot_{II}),



and

$$\text{Rot}_{II(s)} \rightleftharpoons \text{Rot}_{(\text{EtOH})}, \quad (3)$$

we have two ΔF^0 values:

$$\Delta F_I^0 = F^0(\text{Rot}_{(\text{EtOH})}) - F^0(\text{Rot}_{I(s)}) \quad (4)$$

and

$$\Delta F_{II}^0 = F^0(\text{Rot}_{(\text{EtOH})}) - F^0(\text{Rot}_{II(s)}). \quad (5)$$

Note that the $F^0(\text{Rot}_{(\text{EtOH})})$ terms for different polymorphs are the same, so there is only one $F^0(\text{Rot}_{(\text{EtOH})})$ term. This gives rise to two equilibrium constants:

$$\Delta F_I^0 = -RT \ln(K_I) \quad (6)$$

and

$$\Delta F_{II}^0 = -RT \ln(K_{II}). \quad (7)$$

Rearranging and taking the exponential leads to

$$\exp(-\Delta F_I^0/RT) = K_I \quad (8)$$

and

$$\exp(-\Delta F_{II}^0/RT) = K_{II}. \quad (9)$$

Dividing now one by the other leads to

$$\frac{\exp(-\Delta F_I^0/RT)}{\exp(-\Delta F_{II}^0/RT)} = \frac{K_I}{K_{II}}. \quad (10)$$

Because

$$\exp(a)/\exp(b) = \exp(a) \times \exp(-b) = \exp(a - b), \quad (11)$$

we have

$$K_I/K_{II} = \exp \left[(-\Delta F_I^0/RT) - (-\Delta F_{II}^0/RT) \right]. \quad (12)$$

Substituting

$$\Delta F_I^0 = F^0(\text{Rot}_{(\text{EtOH})}) - F^0(\text{Rot}_{I(s)}) \quad (13)$$

and

$$\Delta F_{II}^0 = F^0(\text{Rot}_{(\text{EtOH})}) - F^0(\text{Rot}_{II(s)}) \quad (14)$$

results in

$$K_I/K_{II} = \exp \left[(-[F^0(\text{Rot}_{(\text{EtOH})}) - F^0(\text{Rot}_{I(s)})]/RT) - [-(F^0(\text{Rot}_{(\text{EtOH})}) - F^0(\text{Rot}_{II(s)}))/RT] \right] \quad (15)$$

$$= \exp \left[(-F^0(\text{Rot}_{(\text{EtOH})}) + F^0(\text{Rot}_{I(s)}))/RT + (F^0(\text{Rot}_{(\text{EtOH})}) - F^0(\text{Rot}_{II(s)}))/RT \right] \quad (16)$$

$$= \exp \left[(-F^0(\text{Rot}_{(\text{EtOH})}) + F^0(\text{Rot}_{I(s)}) + F^0(\text{Rot}_{(\text{EtOH})}) - F^0(\text{Rot}_{II(s)}))/RT \right]. \quad (17)$$

We can now eliminate the two $F^0(\text{Rot}_{(\text{EtOH})})$ terms with opposite signs to get:

$$K_I/K_{II} = \exp \left[(F^0(\text{Rot}_{I(s)}) - F^0(\text{Rot}_{II(s)}))/RT \right] = \exp \left[-(F^0(\text{Rot}_{II(s)}) - F^0(\text{Rot}_{I(s)}))/RT \right]. \quad (18)$$

Furthermore, $F = F^0 + RT \ln(a)$, where a is the activity of the phase. For solids, $a = 1$ and because $\ln(1) = 0$ we get $F = F^0$ for solids, so for $F^0(\text{Rot}_{I(s)})$ and $F^0(\text{Rot}_{II(s)})$ we can use the F values from the FHI-aims calculations.

We show in Supplementary Figure 5 the phonon DOS for all rotigotine forms up to 100 cm^{-1} frequency. It can be seen that all three polymorphs have distinct vibrational spectra in the

THz regime. which essentially determine the vibrational free energy differences.

Lastly, we note that the DSC thermogram of form I, as shown in Supplementary Figure 6, indeed shows a small melting endotherm of form II. This may indicate the partial presence of form II from the start in the sample of form I. Another option would be to crystallize some form II during heating in the DSC measurement. We checked the area of the small form II peak to know its relative contribution. It represents only 0.2% of the pure form II value, meaning that the maximum contamination and hence error in the calculations will be about 0.2%. As a conclusion, we can state that there is an uncertainty on the enthalpy differences derived from the DSC data, but that this possible error is marginal with respect to the obtained agreements.

Supplementary References

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